



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/469,485	12/22/1999	QINJIAN ZHAO	20369Y	5022

210 7590 05/05/2003

MERCK AND CO INC
P O BOX 2000
RAHWAY, NJ 070650907

EXAMINER

FOLEY, SHANON A

ART UNIT	PAPER NUMBER
----------	--------------

1648

17

DATE MAILED: 05/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/469,485

Applicant(s)

ZHAO ET AL.

Examiner

Shanon Foley

Art Unit

1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 March 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-20 is/are pending in the application.
- 4a) Of the above claim(s) 1-7 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 8-20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 16.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

Art Unit: 1648

DETAILED ACTION

In paper no. 15, applicant amended claim 20. Claims 1-20 are pending, claims 1-7 are withdrawn from consideration due to a non-elected invention and claims 8-20 are under consideration.

Continued Prosecution Application

The request filed on 3/3/3 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/469485 is acceptable and a CPA has been established. An action on the CPA follows.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 8-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Builder et al. (US 4,620,948) and Valenzuela et al. (Nature. 1979; 280: 815-819).

The claims are drawn to a method of making a recombinant hepatitis B surface antigen (HbsAg) by obtaining a sterile filtered rHBsAg from cell culture, adding a redox buffer comprising glutathione and oxidative glutathione, incubating the buffer and antigen at a temperature between 34°C to 38°C between 40 to about 240 hours.

Applicant agrees that while one of ordinary skill in the art would have been motivated to correct misfolding, the ordinary artisan would not have had a reasonable expectation for producing the claimed invention. Applicant discusses the results of Wampler et al., which teach

Art Unit: 1648

away from using reduced glutathione to reduce proteins because the buffer did not increase disulfide crosslinking in HBsAg. Applicant also argues that Builder et al. do not use the technique to purify HBsAg.

Applicant's arguments have been fully considered, but are found unpersuasive. The paragraph bridging columns 1-2 on page 6832 of Wampler et al. does not discuss the required temperature or length of time required by the claims. The teachings of Wampler et al. have not been and are not considered under 35 USC § 103 because the reference does not teach or suggest the instant method.

With respect to the teachings of Builder et al., the reference is not limited to one protein. Builder et al. emphasize ensuring immunological activity of any protein upon purification. Builder et al. teach inactivity is due to incorrect folding or conformation before or after intracellular precipitation or during the isolation process, see column 1, lines 58-62. The reference exemplifies ways to recover biologically active protein from cell culture by adding a weak denaturing solution and incubating the protein and buffer at 37° C for 24 hours to permit proper refolding, see column 16, lines 28-55, column 17, lines 24-56, and examples 13 and 14 in columns 29-30. The purified protein exemplified by the method of Builder et al. has a much higher activity than unpurified protein.

Builder et al. does not teach purifying HBsAg. However, Valenzuela et al. establish that immunogenicity of HBsAg strongly depends on the integrity and proper formation of the disulfide bonds within the antigen, see column 1 on page 348 and the first full paragraph on page 349. Valenzuela et al. also teach that HBsAg particles purified from cell culture are more variable in size than human particles, see the paragraph bridging pages 349-350.

Art Unit: 1648

One of ordinary skill in the art at the time the invention was made would have been motivated to purify HBsAg by the method of Builder et al. to ensure proper folding and antigenicity of the protein from cell culture. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for producing a properly folded, antigenic HBsAg protein from cell culture using the method of Builder et al. because the proteins purified by Builder et al. are isolated from cell culture and dissolved protein is incubated overnight with a weak denaturing solution to correct incorrect disulfide bridges. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

Claims 17, 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Builder et al. and Valenzuela et al. as applied to claims 8-16 above, and further in view of Petre et al. (WO 93/24148 A1) for reasons of record.

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Builder et al. and Valenzuela et al. as applied to claims 8-16 and 20 above, and further in view of Even-Chen (US 5,242,812) for reasons of record.

Applicant argues that the teachings of Petre et al. or Even-Chen do not remedy the deficiency of Builder et al. However, it is maintained that there is no deficiency in the teachings of Builder et al. and Valenzuela et al. for reasons discussed above. Therefore, it is maintained that claims 17, 19, 20, and 18 are prima facie obvious in view of the teachings of Builder et al. and Valenzuela et al. in further view of Petre et al. and Even-Chen, respectively.

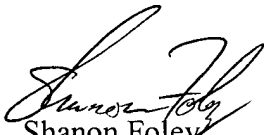
Art Unit: 1648


Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.


Shanon Foley
April 26, 2003


JAMES HOUSEL 5/4/03
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600